

Erasmus MC  
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## Optimizing Dosing Based on PKPD- An overview

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JWM Karlstad 31-05-2018

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## Disclosures

**Research grants – advisory boards – speaker**

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### This Patient Needs Antibiotics. But Which Ones, And Which Dose?

Cartoon removed

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### Dose Finding - The Past

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Signing the amendment of Kefauver and Harris, 1962

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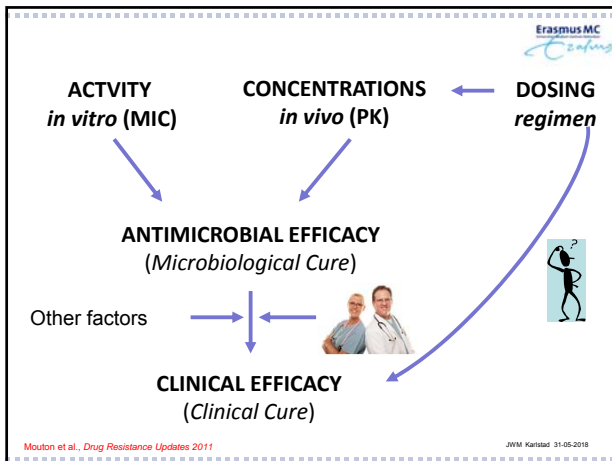
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### Efficacy of the drug

Potency of a drug  
(MIC)

Exposure to the bug  
*In vivo*  
(PK)

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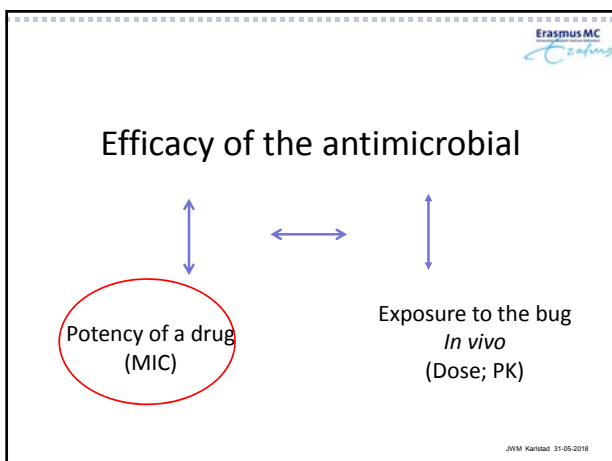
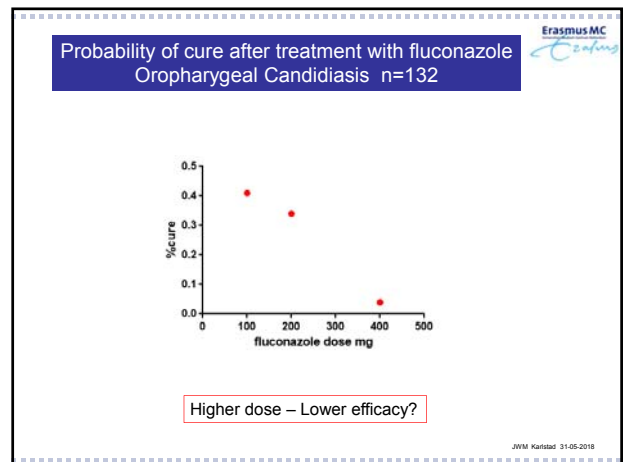
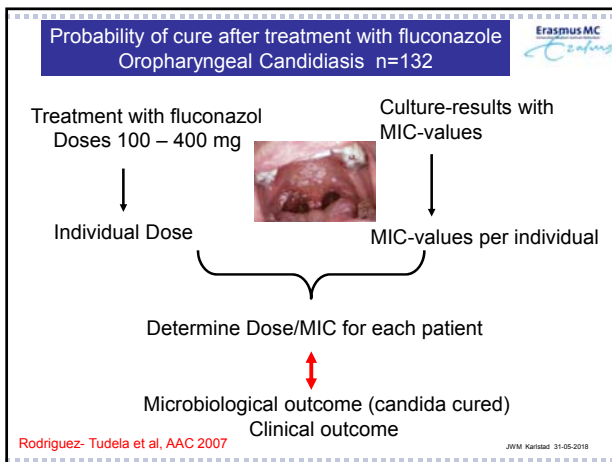


Erasmus MC logo

1st Question:

Does the dose matter?


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2nd Question:

Does the Dose matter  
in relation to the MIC (potency?)?

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### MIC

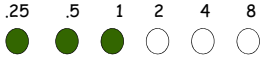
Measure of Potency – antibacterial activity

### MIC

Lowest concentration with no visible growth after 18 hour incubation



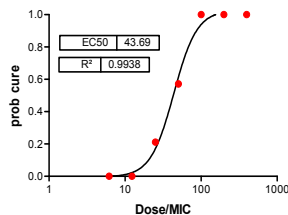
.25 .5 1 2 4 8



MIC = 2 mg/L

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### Probability of cure after treatment with fluconazole Oropharyngeal Candidiasis n=132



EC50 | 43.68  
R<sup>2</sup> | 0.9938

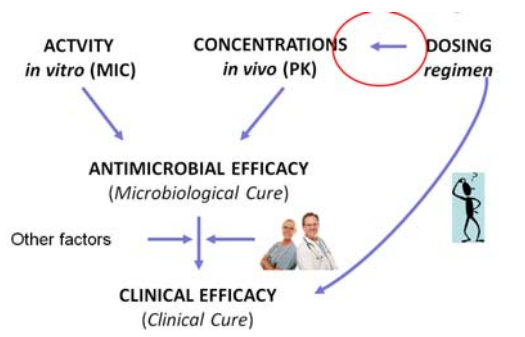
- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez- Tudela et al, AAC 2007

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### Dose is just a means for Exposure



ACTIVITY *in vitro* (MIC)      CONCENTRATIONS *in vivo* (PK)      ← DOSING regimen

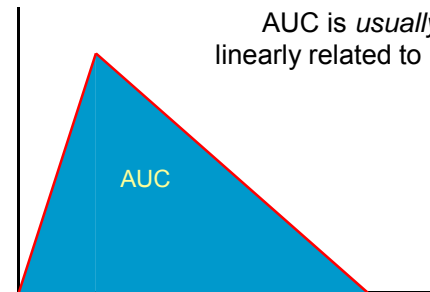

ANTIMICROBIAL EFFICACY (Microbiological Cure)

Other factors      ↓      CLINICAL EFFICACY (Clinical Cure)

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### Pharmacokinetic parameters : Measures of Exposure

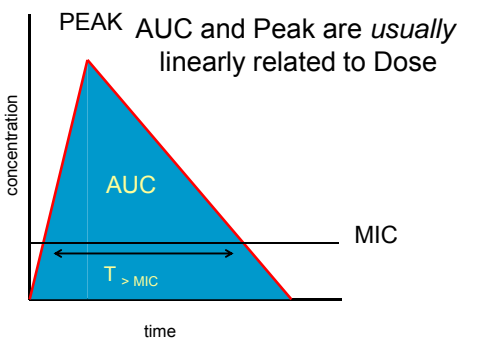
AUC is *usually* linearly related to Dose

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### Pharmacokinetic parameters : Measures of Exposure

PEAK AUC and Peak are *usually* linearly related to Dose



concentration

time

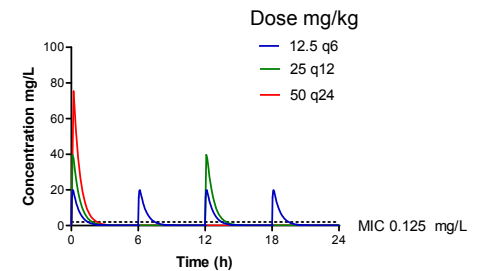
MIC

T > MIC

Mouton et al. 2007 21-44 In Antimicrobial Pharmacodynamics in Theory and Clinical Practice

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### Does the dosing regimen matter?



Dose mg/kg

- 12.5 q6
- 25 q12
- 50 q24

Concentration mg/L

Time (h)

MIC 0.125 mg/L

total length of bars corresponds to Time > MIC

Mouton et al. Drug Resist Updat. 2011 14:107-17

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**Ceftazidime in patients with nosocomial pneumonia**

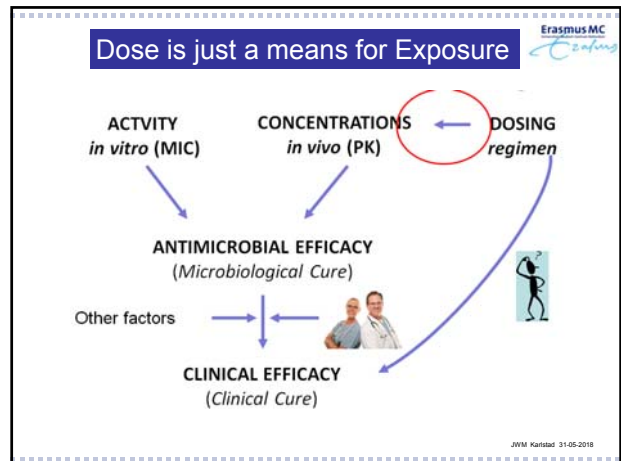
- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion

**N=390 patients included**

**NO clear dose response relationship**

**BUT.....**

Muller et al, JAC 2013 68:900-906



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- randomized, double-blind phase 3 clinical trial (NCT00210964):
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  - Extensive and sparse sampling of ceftazidime**
  - MICs of strains**

**N=390 patients included**

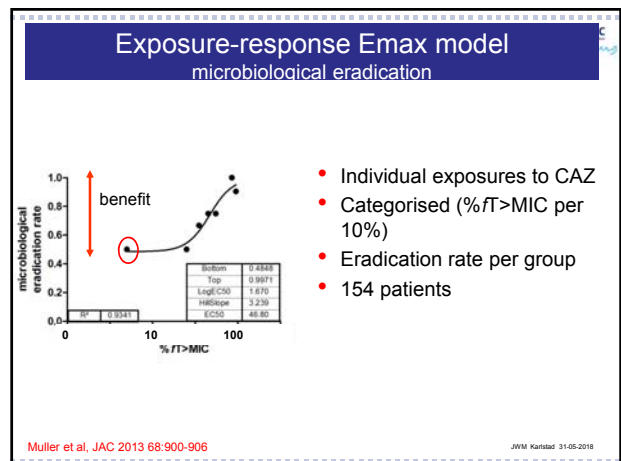
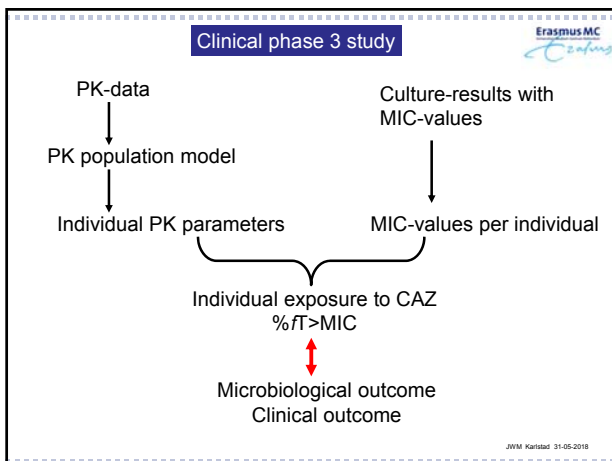
220 without Gram negatives in cultures

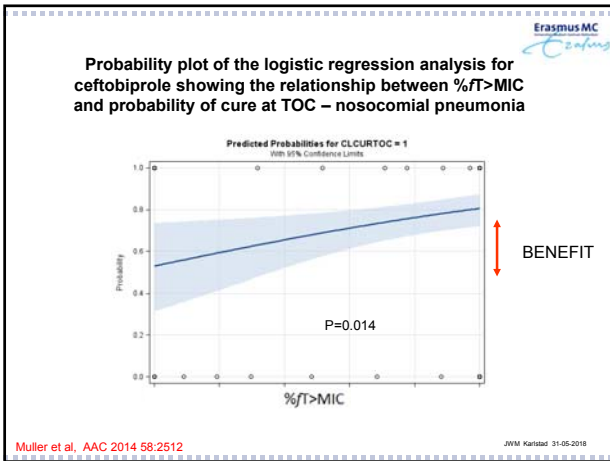
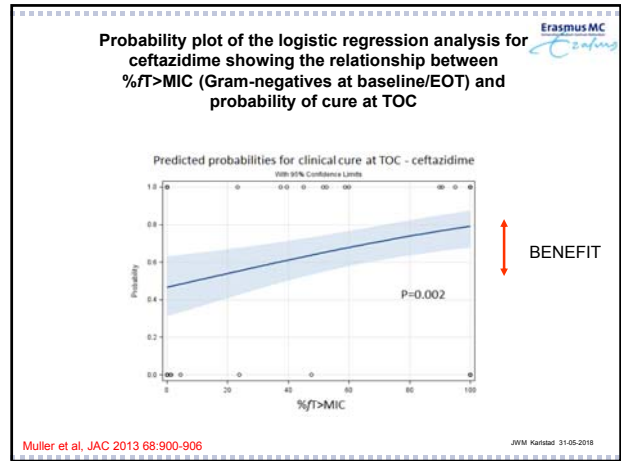
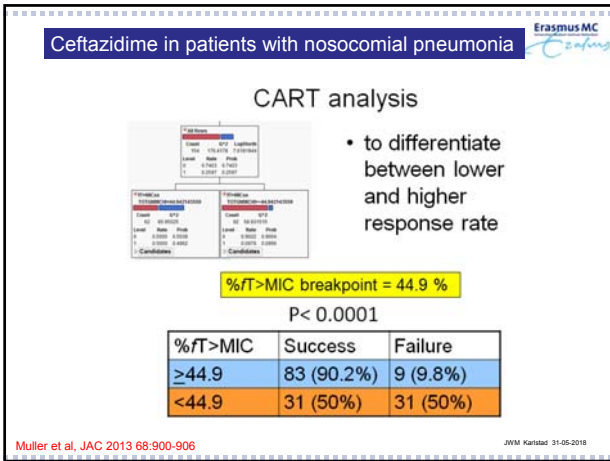
16 without PK estimates

**N=170 with MIC**

**N=154 with MIC and PK-estimates**

Muller et al, JAC 2013 68:900-906





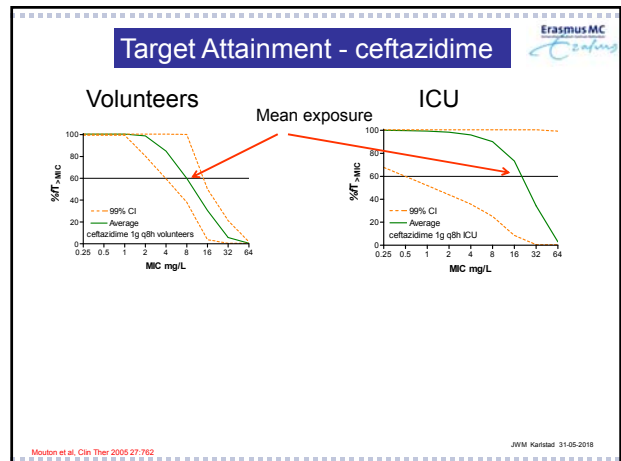
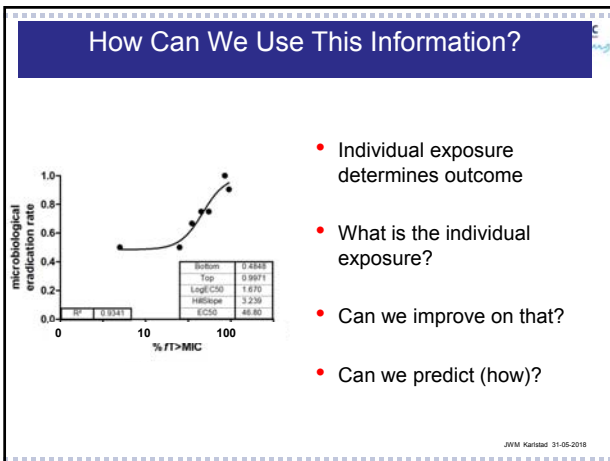
The PKPD relationship is based on MIC AND PK exposure

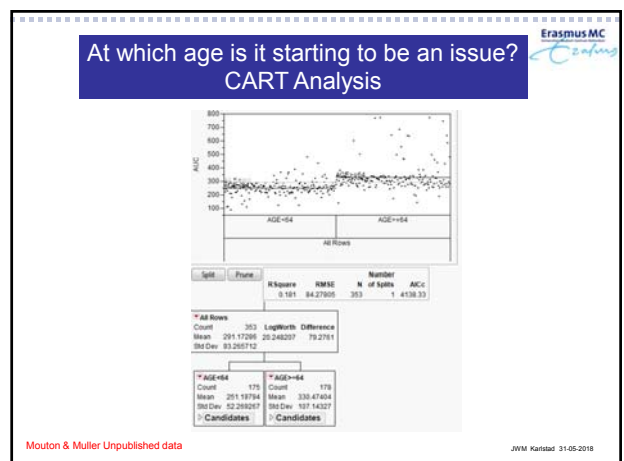
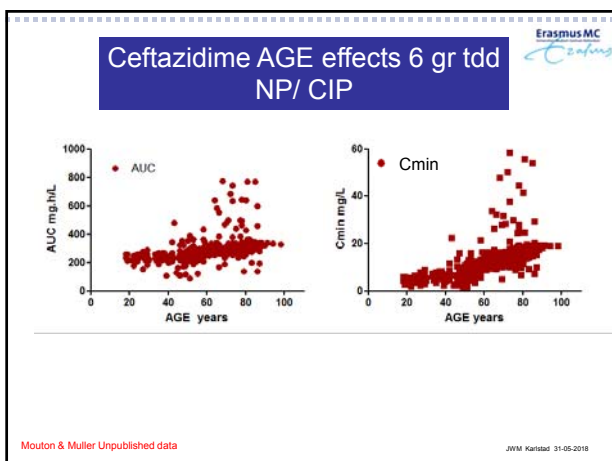
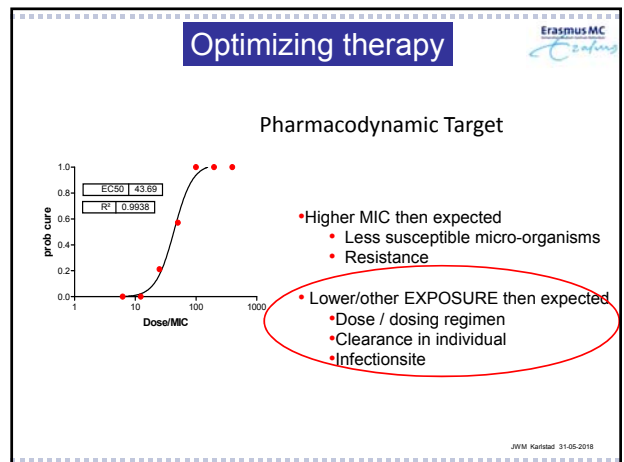
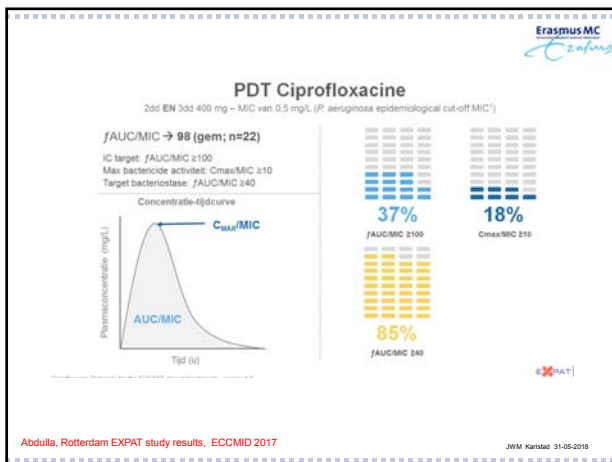
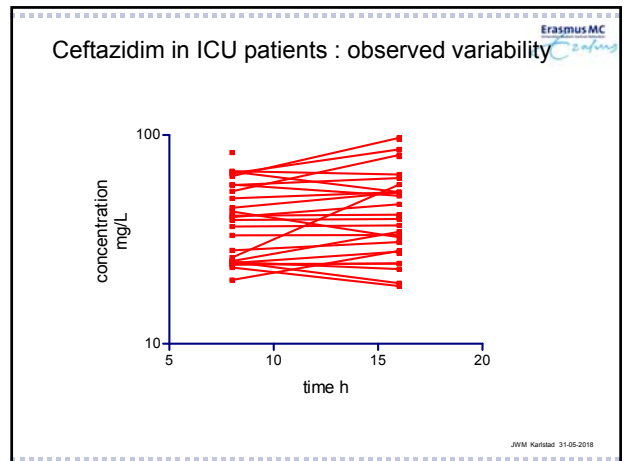
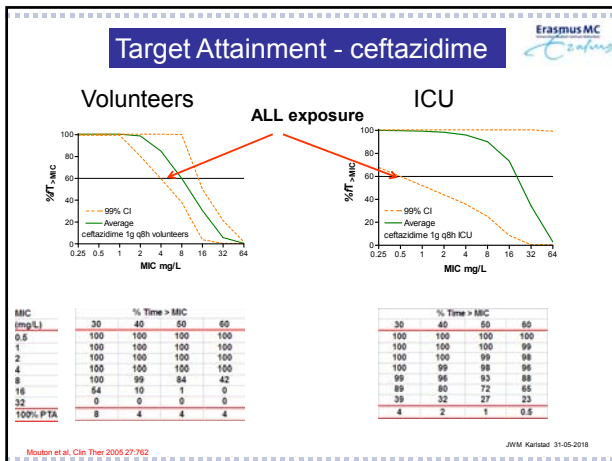
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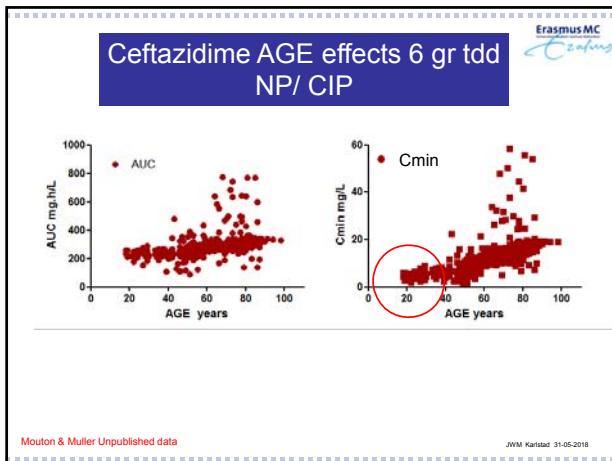
Optimize dose based on:

- Exposure response relationship
- PK characteristics
- MIC (distribution)

Muller et al, AAC 2014 58:2512







### Multiple logistic regression Ceftobiprole, Cure, TOC

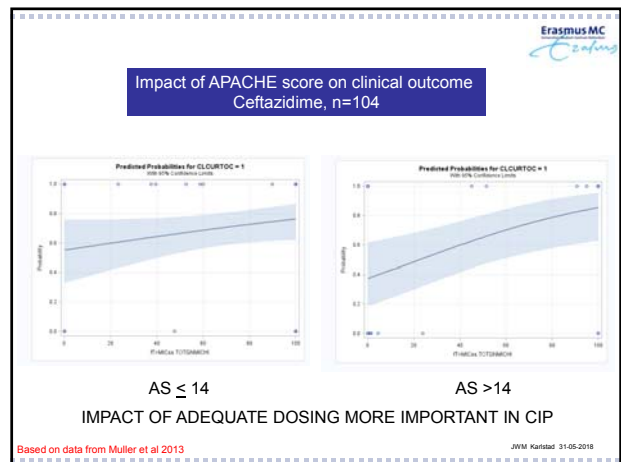
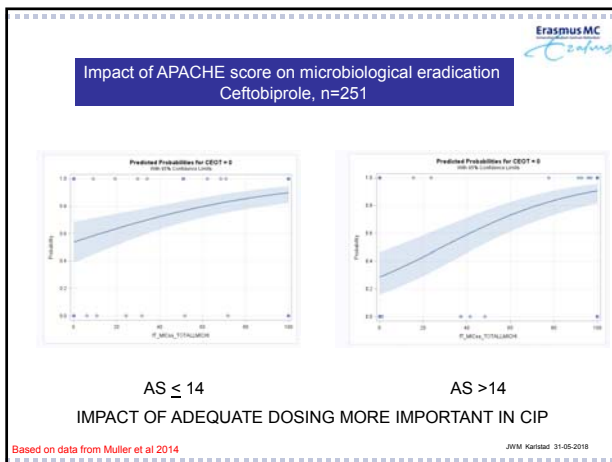
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TABLE 5 Multiple logistic regression analysis of factors determining clinical cure at TOC for all patients

Culture time (n) and covariate	Coefficient	SE	Chi square	P
BL (159)				
Intercept	-0.3157	0.5505	0.3289	0.5663
NP vs VAP patient	-1.9829	0.4611	18.4919	<0.0001
SIRS	1.2103	0.4300	7.9238	0.0049
Anti-Pseudomonas combination therapy	-1.1350	0.4785	5.6256	0.0177
%T>MIC	0.0103	0.00514	4.0376	0.0445
BL/EOT (166)				
Intercept	1.5638	0.6930	5.0926	0.0240
NP vs VAP patient	-2.0851	0.4464	21.8203	<0.0001
%T>MIC	0.0118	0.00431	7.4787	0.0062
APACHE score	-0.0892	0.0429	4.3208	0.0376

Clinical cure at TOC

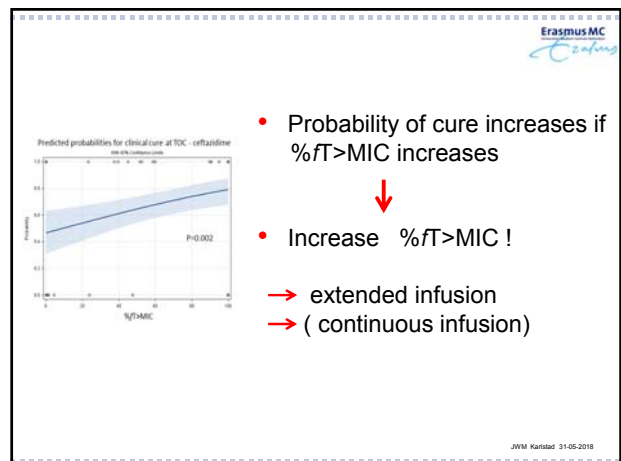
Muller et al. 2014, AAC,58(5):2512  
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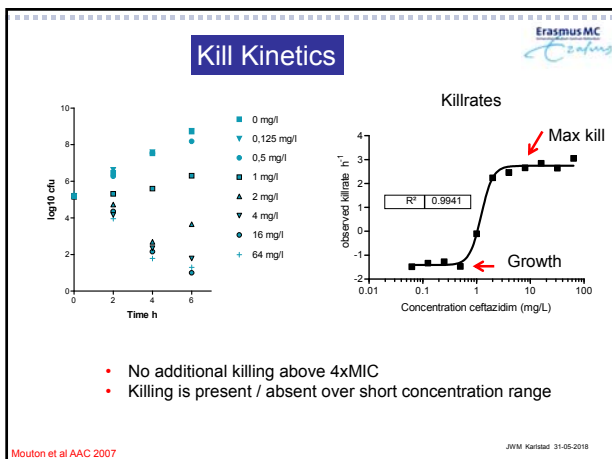
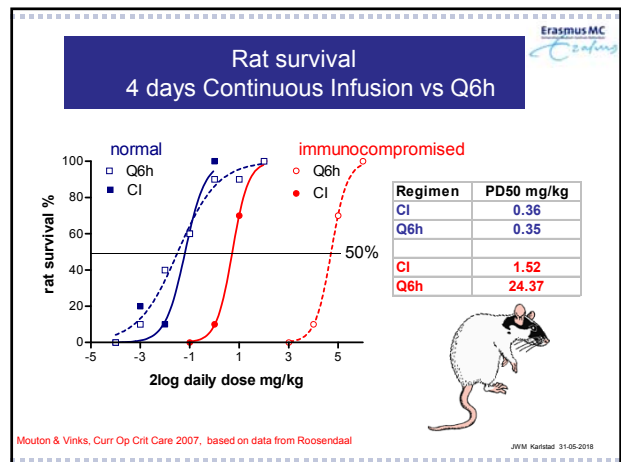
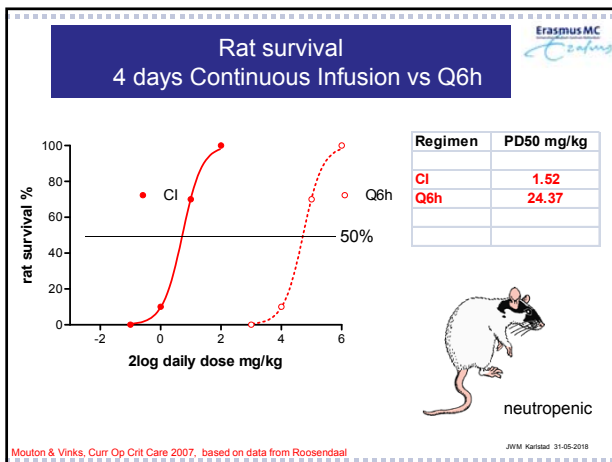
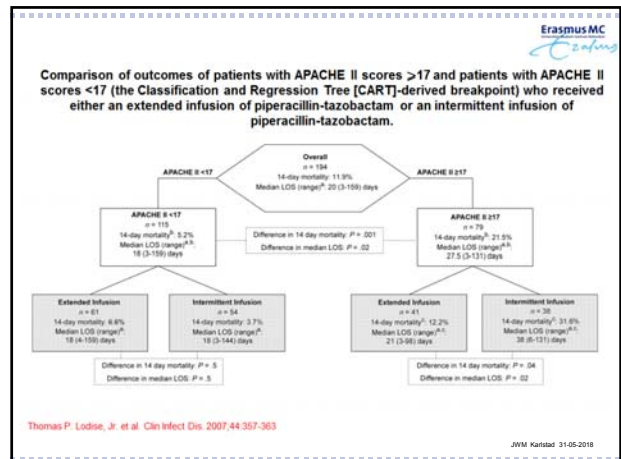
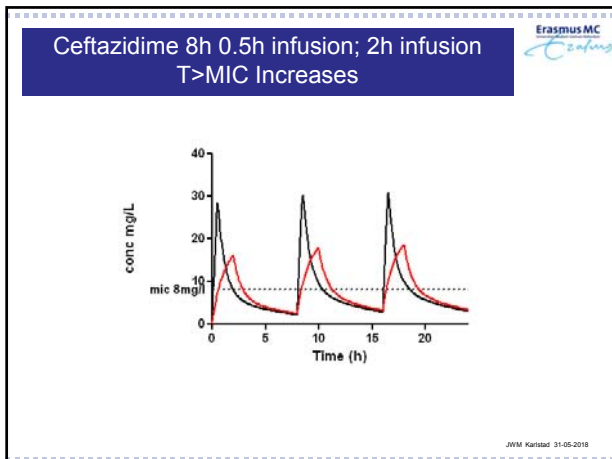


### Strategies to improve target attainment

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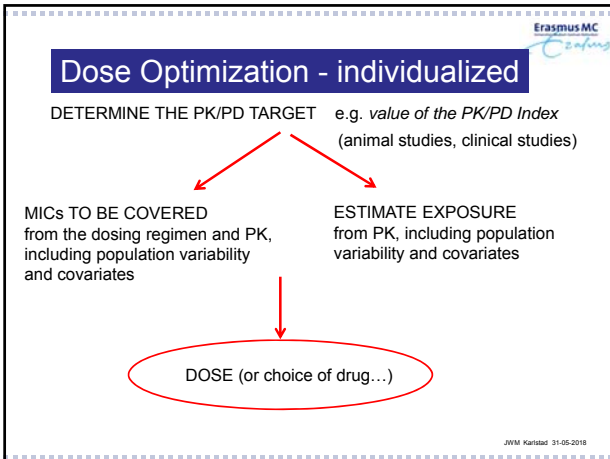
### Continuous vs Intermittent infusion : BLISS study

Primary endpoint	Intervention (n = 70)	Control (n = 70)	Absolute difference (95% CI)	Significance (p value) <sup>†</sup>
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (-0.4 to -0.1)	<b>0.011</b>
Clinical cure by antibiotic, n (%) <sup>†</sup>	22 (58)	15 (32)	26 (-0.4 to -0.1)	<b>0.016</b>
Piperacillin/tazobactam	14 (67)	8 (38)	29 (-0.5 to 0.1)	0.064
Meropenem	3 (27)	1 (50)	23 (-0.3 to 0.7)	1.000
Cefepime	14 (42)	13 (39)	3 (-0.3 to 0.2)	0.802
Clinical cure by concomitant antibiotic treatment, n (%) <sup>†</sup>	25 (68)	11 (30)	38 (-0.6 to -0.2)	<b>0.001</b>
Clinical cure by site of infection, n (%) <sup>†</sup>	27 (59)	12 (33)	25 (-0.4 to -0.1)	<b>0.022</b>
Clinical cure by <i>A. baumannii</i> or <i>P. aeruginosa</i> infection, n (%) <sup>†</sup>	13 (52)	6 (25)	27 (-0.5 to 0.1)	0.052
Yes	13 (52)	6 (25)	27 (-0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (-0.3 to 0.2)	0.655

Abdul-Aziz, Int Care Med 2016 PBP

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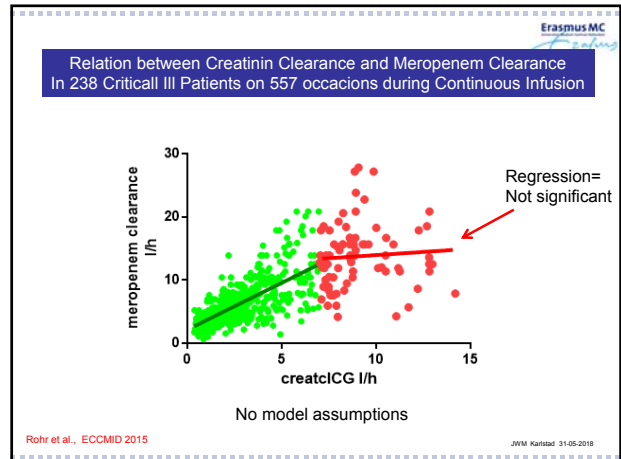
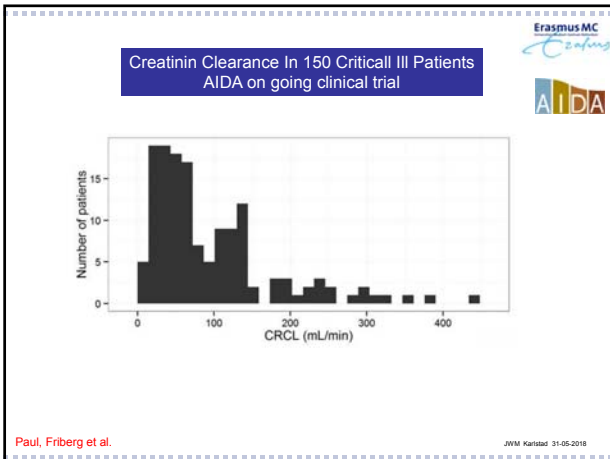




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## Estimate exposure – How can we predict clearance in critically ill?

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## We Need Therapeutic Drug Monitoring for Antibiotics!!!!

- In particular in patients with high/augmented clearance

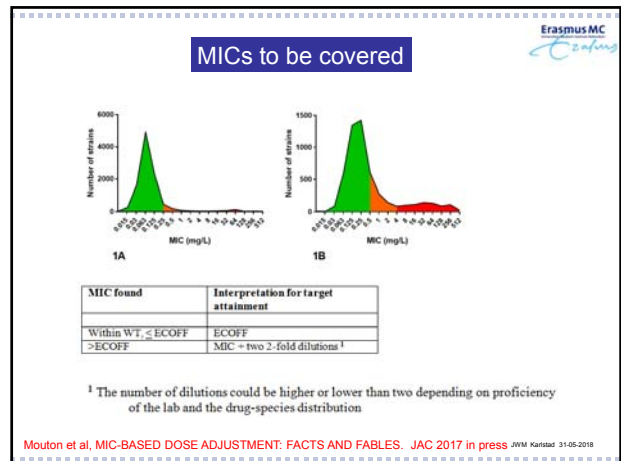
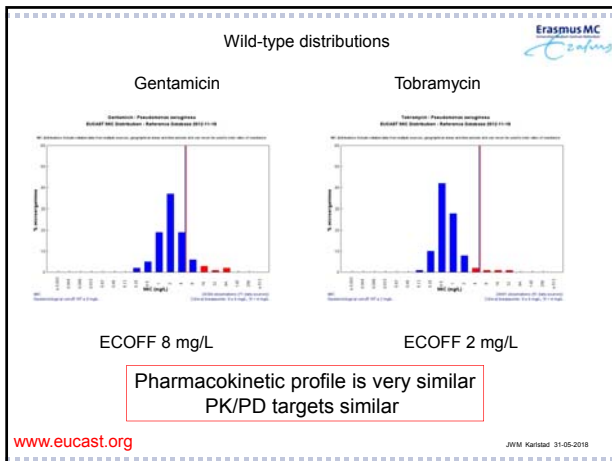
- Development of fast methods to measure drug concentrations TDM!!
- For non-continuous infusion, develop and use population models  
-Analyze covariates

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## And the MIC part of the Equation? How to use that?

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MIC distribution of 14 strains in 5 labs in quadruplicate  
Linezolid, *S.aureus*

MIC mg/L	strain code (occurrences)													
	A	b	c	D	e	f	h	i	j	K	L	M	N	O
0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0.5	0	0	0	0	0	5	0	0	0	0	0	0	0	0
1	0	5	6	0	12	14	3	14	11	0	3	1	0	3
2	16	15	13	10	7	1	13	6	9	8	14	15	7	14
4	4	0	1	10	1	0	4	0	0	11	3	4	13	2
8	0	0	0	0	0	0	0	0	0	1	0	0	0	0
<b>Total</b>	20	20	20	20	20	20	20	20	20	20	20	20	20	20
<b>Mode</b>	2	2	2	2	1	1	2	1	2	4	2	2	4	2
<b>Geomean</b>	2.30	1.68	1.68	2.83	1.37	0.87	2.07	1.23	1.37	3.14	2.00	2.22	3.14	1.74
<b>Range</b>	2	2	3	2	3	3	3	2	2	3	3	3	2	5

Mouton et al. Variation of MIC measurements: the contribution of strain and laboratory variability to measurement precision JAC 2018, in press JWM Karlstad 31-05-2018

- Conclusions
- PK/PD explains and predicts the effects of antimicrobials
  - For beta-lactams, %T>MIC is the most important predictor; for most other drugs it is fAUC/MIC
  - Increasing %T>MIC to increase target attainment by adjusting the dosing regimens, TDM should be performed if no good prediction can be made
  - Dosing regimens optimal for exposure may select for resistance / adjustments are clearly required
  - Choose the right drug!
- JWM Karlstad 31-05-2018